

# Doxycycline in the single-dose treatment of gonorrhoea

## Effect on *Treponema pallidum*

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Single-dose treatment is a proved method of therapy for acute gonorrhoea in the male. In recent years we have tested the antibiotics penicillin and thiamphenicol used in single doses and have obtained good results. In patients treated with injections of 4 m.u. penicillin (3.6 crystalline plus 0.4 clemizol-penicillin) failures occurred in 7.4 per cent., and in those treated with 2.5 g. thiamphenicol by mouth in 5.8 per cent. (Petzoldt, 1971).

Comparatively few reports on the treatment of gonorrhoea with doxycycline have so far been published. Failure rates have ranged between 3.6 and 14.3 per cent. (Lassus, 1968; Domescik, McLone, Scotti, and Mackey, 1969; Lidén, Hammar, Hillström, Wallin, and Ohman, 1971; Schaller and Kulenkamp, 1971). In another investigation treatment with doxycycline of patients infected by strains of gonococci with decreased sensitivity to penicillin resulted in a failure rate of 17 per cent. (Lassus, 1970).

This paper reports our clinical experiences with doxycycline, and the results of animal experiments designed to determine whether a single dose of doxycycline is able to cure a simultaneously acquired syphilis.

### Material and methods

#### I. CLINICAL INVESTIGATIONS

300 mg. doxycycline were given orally to each of 129 male patients with acute uncomplicated gonococcal urethritis. The capsules\* were swallowed with water in the presence of a physician or nurse. In all cases the diagnosis was confirmed by the microscopic examination of smears and by culture. Follow-up smears and cultures were taken usually after 3, 6, and 13 days. Failures were diagnosed when gonococci were found within 7 days after treatment. In view of the unreliability of the patients' statements regarding further sexual contact no attempt was made to differentiate between relapse and re-infection at this early stage after treatment.

#### II. EXPERIMENTAL INVESTIGATIONS

21 male rabbits weighing 2.5–3 kg. were infected intratesticularly with a suspension of 300 treponemes of the Nichols strain of *T. pallidum* according to the method of Morgan and Vryonis (1938). Treponemes were suspended in 0.2 ml. of a medium consisting of:

Component	Percentage
Rabbit-serum (inactivated)	25.0
Na <sub>2</sub> HPO <sub>4</sub>	0.18
KH <sub>2</sub> PO <sub>4</sub>	0.025
Sodium pyruvate	0.005
Sodium thioglycollate	0.06
Cystein hydrochloride	0.01
NaHCO <sub>3</sub>	0.03
Glutathione (reduced)	0.015
0.9 per cent. NaCl	ad 50.0

3 days after infection fourteen of the rabbits were treated with doxycycline. In order to achieve serum levels in the laboratory animals similar to those in patients who had received 300 mg. in a single dose (Fig. 1), it was necessary to inject doxycycline intravenously in multiple doses. A total amount of 240 mg. doxycycline divided into eight doses proved to be suitable. It was given as 40 mg. 6-hrly for four doses, followed by 20 mg. 5-hrly for four doses. Doxycycline serum levels were determined by serial dilution tests using *Staph. aureus* ATCC 6538 P. The sensitivity was 0.032 µg./ml.

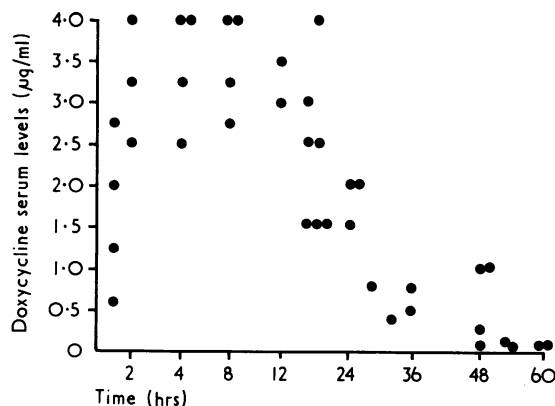


FIG. 1 Doxycycline serum levels in man after a single oral dose of 300 mg.

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After treatment, the rabbits were examined at weekly intervals for clinical and serological signs of developing syphilis. The testicles were palpated and quantitative serum FTA-ABS tests were carried out. When a testicular infiltrate was found, a biopsy was taken in order to detect the presence of treponemes by darkfield examination. The study was concluded 14 weeks after the initial inoculation.

## Results

### I. CLINICAL RESULTS

Doxycycline was well tolerated, except that two patients vomited the capsules after about 30 min. Of the 129 patients followed, 117 were cured and twelve (9.3 per cent) relapsed or were re-infected.

### II. EXPERIMENTAL RESULTS

After an incubation period of 4 to 6 weeks all the rabbits developed a syphilitic orchitis, and the titres of the FTA-ABS tests increased.

There was a distinct difference between the rabbits treated with doxycycline and the untreated controls. Both syphilitic orchitis and increasing FTA-ABS titres appeared 1 to 2 weeks later in the treated animals than in the untreated controls (Fig. 2); 13 weeks after inoculation FTA-ABS titres ranged between 6,400 and 102,400.

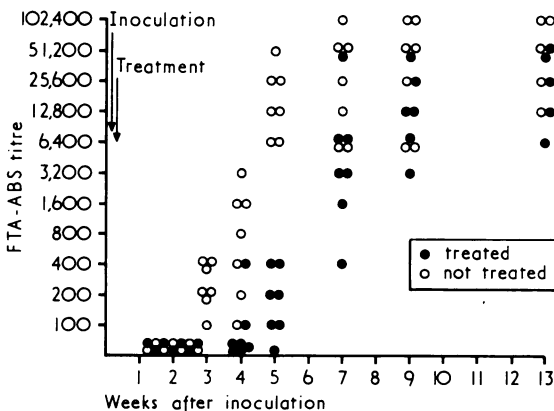


FIG. 2 FTA-ABS titres in experimental syphilis in rabbits

## Discussion

The advantage of single-dose treatment of acute gonorrhoea is the convenience for both patient and physician, and several antibiotics are suitable for use in this way. When doxycycline was administered in a single oral dose of 300 mg., the failure rate was 9.3 per cent. This seems to be comparatively high,

but it includes both relapses and possible re-infections within 7 days after treatment.

In previous studies we ascertained that the results of treatment with multiple doses of penicillin are superior to those using a single dose of penicillin or thiamphenicol (Petzoldt, 1972). The failure rate of 3.4 per cent. obtained with multiple doses of penicillin compared with 9.3 per cent. obtained with a single dose of 300 mg. doxycycline indicates once more the superiority of our conventional therapeutic schedule. Therefore we do not wish to recommend the single dose of doxycycline as a routine treatment for gonorrhoea.

Previous experimental investigations have shown that single doses of penicillin or thiamphenicol are able to cure a very early incubating syphilis (Petzoldt, 1971). This means that, in cases of double infection with gonorrhoea and syphilis, a single dose of these antibiotics is sufficient to cure both acute gonorrhoea and a simultaneously acquired syphilis.

The results of the present study, however, show that a single dose of doxycycline has little effect on *Treponema pallidum*; doxycycline was not able to cure incubating syphilis in the rabbit when administered in a dosage corresponding to a single dose of 300 mg. in man.

It is interesting that both the syphilitic orchitis and the increasing FTA-ABS titres appeared 1 to 2 weeks later in the animals treated with doxycycline than in the untreated controls. This shows that doxycycline did indeed diminish the number of inoculated treponemes, but did not eradicate them, so that a single dose of doxycycline given for gonorrhoea would not cure a simultaneously acquired syphilis. This conclusion, based on our experimental investigation, agrees with the statistical analysis carried out by Schroeter, Turner, Lucas, and Brown (1971) in man.

## Summary

129 male patients with acute gonorrhoea were treated with a single oral dose of 300 mg. doxycycline. The failure rate, including relapses and re-infections within 7 days after treatment, was 9.3 per cent.

Experiments were performed on rabbits to determine if this dose of doxycycline could cure a simultaneously acquired syphilis at a very early stage of incubation. 300 treponemes (Nichols strain *T. pallidum*) were inoculated intratesticularly and 3 days later doxycycline was administered in doses which produced doxycycline serum levels similar to those in patients who had received a single oral dose of 300 mg.

This dosage of doxycycline did not prevent the development of syphilitic orchitis or reactivity to the FTA-ABS test. It is concluded that the treatment of acute gonorrhoea with 300 mg. doxycycline is not sufficient to cure a simultaneously acquired syphilis.

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## La doxycycline en dose unique dans le traitement de la gonococcie. Son effet sur *Treponema pallidum*

### SOMMAIRE

129 hommes atteints de gonococcie aigüe furent traités par une dose orale unique de 300 mg de doxycycline. Le taux d'échec, comprenant les rechutes et les réinfections, fut de 9,3 pour cent dans les 7 jours suivant le traitement.

Des expériences furent faites sur le lapin pour établir si cette dose de doxycycline pouvait guérir une syphilis acquise simultanément et au stade très précoce de l'incubation. 300 tréponèmes (souche Nichols de *T. pallidum*) furent inoculés par voie intra-testiculaire et 3 jours plus tard la doxycycline fut administrée à des doses donnant des taux sériques semblables à ceux trouvés chez les malades qui avaient reçu une dose orale unique de 300 mg.

Cette posologie de la doxycycline n'eût pas d'action préventive sur le développement de l'orchite syphilitique ni sur la positivité du test FTA-ABS.

On conclut que le traitement de la gonococcie aigüe par une dose unique de 300 mg de doxycycline n'est pas suffisant pour guérir une syphilis acquise en même temps.